Cerebral Venous Thrombosis
Combined Intrathrombus rtPA and Intravenous Heparin

James L. Frey, MD; Gerard J. Muro, MD; Cameron G. McDougall, MD; Bruce L. Dean, MD; Heidi K. Jahnke, RN, BSN

Background and Purpose—We chose to evaluate the safety and efficacy of combined intrathrombus rtPA and intravenous heparin in cerebral venous thrombosis (CVT).

Methods—We treated 12 patients with symptoms of 1 to 40 days’ duration (eg, headache, somnolence, focal deficits, seizures, and nausea and vomiting). Pretreatment MRI disclosed subtle hemorrhagic venous infarction in 4 patients, obvious hemorrhagic infarction in 2, small parenchymal hemorrhage from recent pallidotomy in 1, and no focal lesion in 5. Magnetic resonance venography and contrast venography identified thrombi in the superior sagittal sinus (SSS) in 3 patients; transverse/sigmoid sinus (TS/SS) in 2; SSS and both TS/SS in 1; SSS and 1 TS/SS in 5; and SSS, 1 TS/SS, and straight sinus in 1 patient. A loading dose of rtPA was instilled throughout the clot at 1 mg/cm, followed by continuous intrathrombus infusion at 1 to 2 mg/h. Intravenous heparin was infused concomitantly.

Results—Flow was restored completely in 6 patients and partially in 3, with a mean rtPA dose of 46 mg (range, 23 to 128 mg) at a mean time of 29 hours (range, 13 to 77 hours). Symptoms improved in these 9 patients concomitantly with flow restoration. Flow could not be restored in 3 patients. In 1 of them, treatment was stopped when little progress had been made, and fibrinogen level dropped to 118 mg/dL. In the other 2 patients, hemorrhagic worsening occurred, and treatment was abbreviated after initial rtPA dosing. In 1 of these, the hematoma was evacuated.

Conclusions—Our experience with intrathrombus rtPA in conjunction with intravenous heparin in patients with CVT is encouraging. This therapy should probably be regarded as unsafe in patients with obvious hemorrhage. Time to restore flow may be faster than with urokinase (an average of 71 hours has been reported for 29 documented patients). Further evaluation of rtPA with heparin in CVT is warranted. (Stroke. 1999;30:489-494.)

Key Words: plasminogen activator, tissue type I thrombolytic therapy I venous thrombosis

Cerebral venous thrombosis (CVT) is an uncommon condition that often has severe clinical consequences.1–4 Available data suggest that treatment with intravenous heparin improves outcome.4–8 However, these data come largely from nonrandomized, uncontrolled, and nonblinded studies. Experience with intravenous urokinase has been limited.3,9–13 Treatment with direct intrathrombus urokinase has been associated with effective thrombus dissolution and the potential for improved outcome.14–28 However, mean time required to restore flow in 29 documented cases was 71 hours.14,16,17,19,20,22–27

Despite its greater clot specificity and the potential for efficacy with fewer hemorrhagic complications than urokinase, recombinant tissue plasminogen activator (rtPA) has been used less extensively and only more recently. The first reported use of direct intrathrombus administration of rtPA in 3 patients demonstrated clinical and technical efficacy, reported no complications, and disclosed an average treatment time of 32 hours.29 A second series documented technical efficacy in 9 patients (“successful recanalization with improvement of symptoms was achieved in all cases”) and reported an average treatment time of 18 hours.30 Concomitant intravenous heparin was used in both series. In a third single case report, technical efficacy and favorable outcome were reported at 24 hours after treatment.31 Concomitant intravenous heparin was not used.

We sought to evaluate direct intrathrombus rtPA in combination with intravenous heparin and to assess the safety, efficacy, and potential cost-effectiveness of this regimen. We report herein our experience, emphasizing both technical and clinical outcomes and time required for treatment.

Subjects and Methods
We treated 12 consecutive patients, 9 women and 3 men, ranging in age from 20 to 47 years. All patients had symptoms, deficits, or both that were clinically disabling and nonresolving or worsening. Eligibility for treatment was the same as for intravenous heparin alone. Presenting manifestations occurred over 1 to 40 days (average, 10 days) and included headache,12 focal neurological deficits,9 somnolence,3 seizures,3 and nausea and vomiting4 (Table1).
All patients were studied with CT brain scan, MRI, magnetic resonance venography (MRV), and contrast venography. Thrombi were identified in the superior sagittal sinus (SSS) alone in 3 patients; transverse/sigmoid sinus (TS/SS) in 2; SSS and both TS/SS in 1; SSS and 1 TS/SS in 5; and SSS, 1 TS/SS, and straight sinus (ST.S) in 1. MRI before treatment revealed subtle hemorrhagic venous infarction in 4 patients (small or indiscernible on CT), small deep hemorrhage caused by recent pallidotomy in 1 patient, and more obvious hemorrhagic infarction in 2 patients. MRI was negative in 5 patients.

After informed consent had been obtained, thrombosis was confirmed by transfemoral contrast venography. A microcatheter was advanced rostrally through the thrombus, and contrast was injected to define the extent of the lesion. One-milligram boluses of rtPA were then instilled at 1- to 2-cm intervals as the microcatheter was withdrawn caudally through the length of the thrombus. The microcatheter was then readvanced to the rostral segment of the thrombus, and rtPA infusion was continued at 1 to 2 mg/h.

All patients received concomitant intravenous heparin to achieve therapeutic anticoagulation (partial thromboplastin time [PTT] twice control). Fibrinogen levels and PTT were checked every 12 hours. Patients were monitored in intensive care.

The radiological effect of treatment was reassessed with contrast venography at 12- to 24-hour intervals. The microcatheter was repositioned to remain within the thrombus at a distance of 2 to 3 cm from the rostral end of the thrombus. rtPA infusion was discontinued on the basis of documentation of flow restoration, even if residual thrombus was present. All patients were studied with posttreatment CT or MRI within 12 hours. Heparin anticoagulation was maintained, and patients were converted to warfarin therapy.

The clinical effect of treatment was gauged by standard neurological examination and length of stay from the beginning of treatment. Outcomes were determined as of the date of discharge and at long-term follow-up.

Coagulopathy evaluations included prothrombin time, PTT, activated protein C resistance, levels of proteins C and S and antithrombin III (measured as percent activity), lupus anticoagulant, and anticardiolipin antibody.

Results

Flow was restored completely in 6 patients, with symptom resolution in 5 (patients 3, 4, 6, 7, and 10) and symptom improvement in 1 (patient 8). In 1 patient (patient 8), optic nerve decompression was performed to relieve intracranial pressure 24 hours after initiation of treatment. Thrombotic therapy and intravenous heparin were suspended for 12 hours to accommodate surgery. This patient sustained visual impairment from retinal damage secondary to papilledema.

<table>
<thead>
<tr>
<th>Technical Outcome</th>
<th>Average Dose/Rx Time</th>
<th>Recovery</th>
<th>Partial</th>
<th>No Δ</th>
<th>LOS†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete flow restoration</td>
<td>6</td>
<td>49 mg/31 h</td>
<td>23–128 mg/13–77 hr</td>
<td>5</td>
<td>1†</td>
</tr>
<tr>
<td>Incomplete flow restoration</td>
<td>3</td>
<td>40 mg/26 h</td>
<td>24–55 mg/14–32 h</td>
<td>2</td>
<td>1†</td>
</tr>
<tr>
<td>No flow restoration</td>
<td>3</td>
<td>35 mg/12 h</td>
<td>10–58 mg/0.5–33 h</td>
<td>0</td>
<td>2‡ (1*)‡</td>
</tr>
</tbody>
</table>

Rx indicates treatment Δ; LOS, length of stay. Values are mean (range).
*Hemorrhagic worsening.
†Mean days from beginning of rtPA treatment.
‡Improved and functionally independent at 6 mo.
§Improved and functionally independent at 1 mo.
Flow restoration was incomplete in 3 patients (patients 2, 5, and 11). In patients 2 and 11, the SSS was opened, but further treatment of the occluded TS/SS was foregone because all symptoms had resolved. In patient 5, the occluded TS was opened with residual thrombus in the lumen. The patient’s headache resolved in conjunction with flow restoration, but she had persistent language dysfunction from a left temporal lobe hemorrhagic infarction that had occurred 9 days before treatment.

Flow was not restored in 3 patients. In patient 1, the catheter could not be advanced beyond the sigmoid sinus, presumably because of the age and degree of “organization” of the thrombus. Although rtPA infusion did reduce the length of the thrombus, low fibrinogen level (118 mg/dL) precluded continuation of therapy. Heparin was continued, and the patient’s deficits improved gradually. Her seizures were controlled with anticonvulsant medication. MRV 11 days after treatment revealed flow improvement in her previously partially occluded SSS and flow restoration in her completely occluded left TS/SS. She was functionally independent at hospital discharge 20 days after treatment.

The other 2 patients in whom flow was not restored sustained hemorrhagic worsening related to treatment. In 1 of these, patient 9, the loading dose of rtPA had been administered, but continued rtPA infusion and intravenous heparin were not administered out of concern for the presence of a 23-cc hemorrhagic lesion on pretreatment CT (Figure 1A).

Figure 1. A, From patient 9, CT immediately before treatment revealed prominent hemorrhagic component. B, From patient 9, CT 12 hours after bolus rtPA infusion revealed enlarged area of hemorrhage with extension into lateral ventricle. C, From patient 9, CT after evacuation of hemorrhage and placement of ventricular drain.

Twelve hours subsequent to rtPA loading dose the patient’s condition had worsened, and repeat CT brain scan disclosed an increase in the hemorrhagic component of the brain lesion with extension into the ventricle (Figure 1B). The hematoma was evacuated uneventfully (Figure 1C). The patient received no warfarin anticoagulation and was provided with rehabilitation. Her condition at discharge had improved compared with admission examination, with slight residual right hemiparesis at 20 days. MRV 2 months later revealed restored flow in the SSS. The patient required anticonvulsant treatment for seizure control but made a full recovery and returned to her previous employment.

In the other case (patient 12), intravenous heparin was begun, and loading-dose rtPA was infused into the SSS, left TS/SS, and ST.S. Treatment was stopped because the patient’s neurological deficits worsened 1 hour after the rtPA loading dose. At that time, CT brain scan revealed enlargement of his pretreatment 14-cc hemorrhagic lesion. Over the next 18 hours, the patient remained clinically stable, and repeat CT brain scan revealed no change. Contrast venogram revealed no change in the SSS thrombosis but improved flow within the left TS/SS and ST.S. The patient was retreated with loading dose rtPA infusion into the SSS alone. He remained clinically stable, and CT brain scan 3 hours later was unchanged. At that time, intravenous heparin was begun, but further rtPA infusion was withheld. The patient remained stable, and warfarin therapy was begun 2 days after treatment.

At the time of discharge, 12 days after treatment, his right hemiparesis was worse than before treatment, and his language dysfunction was unchanged. MRV at 4 days posttreatment revealed continued absence of flow in the SSS and left TS/SS sinus. After rehabilitation, he was functionally independent at 30 days.

Other complications during treatment included a groin hematoma in patient 6, which was managed with cessation of rtPA and heparin for 1 hour, and head/neck pain ipsilateral to the infusion catheter in patients 1, 6, and 11, which required narcotic analgesia intermittently.

Average duration of rtPA infusion was 30 hours (range, 13 to 77 hours). Average rtPA dose was 43 mg (range, 10 to 128 mg). Duration of hospitalization from time of treatment onset was 9 days (range, 4 to 20 days). Duration of hospitalization was protracted in patients 1, 8, 9, and 12 (20, 10, 20, and 12 days, respectively). Reasons for delay were treatment and adjustment of seizure medication in patient 1; delay in arranging outpatient home support for patient 8; pneumonia requiring treatment in patient 9; and continued lethargy with slow improvement in patient 12. In all other patients, the
duration of hospitalization from the beginning of treatment (average 6 days) primarily reflected time for adjustment of warfarin therapy.

The 4 patients who required the highest doses of rtPA were those whose symptoms were of the longest duration (patient 2, 15 days; patient 11, 21 days; patient 1, 23 days; and patient 8, 41 days). No patient developed symptoms of thrombosis return during average follow-up of 10 months (range, 1 to 30 months).

The presumed cause of thrombosis was oral contraceptives in 2 patients (patients 2 and 7), status postpartum in 2 (patients 1 and 11), hypercoagulability secondary to surgery in 2 (patients 6 and 8), protein S deficiency in 1 (patient 5), lymphomatous meningitis treated with brain radiation and intrathecal chemotherapy in 1 (patient 4), vertex head trauma in 1 (patient 3), and uncertain in 3 (patients 9, 10, and 12).

Discussion

Our most important safety observation from this study relates to the possibility that treatment caused or contributed to hemorrhagic worsening in patients 9 and 12. We cannot tell whether the worsening in these patients was simply a consequence of the natural evolution of the lesion, which was less than 24 hours old in both, and we cannot differentiate between the effect of heparin versus rtPA as contributors to the worsening in patient 12. Nonetheless, it seems reasonable to presume that rtPA may have contributed to hemorrhagic worsening in both of these cases. The difference between these 2 patients and the 4 others who had parenchymal hemorrhage on pretreatment MRI is that there was a greater volume of blood in these 2. For the moment, an important caveat in considering this treatment is that the presence of hemorrhage in the 14-mL range on CT scan probably contraindicates the use of intrathrombus rtPA. This is in contrast to a previous report of treatment with direct infusion of urokinase in which no brain hemorrhagic complications occurred despite the presence of pretreatment hemorrhage in 4 of 13 patients.19

Another safety concern relates to the size and severity of ischemic/congestive change on CT scan. Patient 5 sustained symptom onset 12 days before treatment and at the time of treatment had the largest area of ischemic/congestive change on brain scan, which included a hemorrhagic component (Figure 2). Despite the favorable treatment results in this patient, the safety of rtPA in patients with large ischemic/congestive lesions remains to be determined.

In the 10 patients in whom the complete treatment protocol could be pursued, catheter penetration of the thrombus was possible in 9. Flow restoration was obtained in these 9 patients; outcomes were favorable; and duration of hospitalization was relatively short (average, 6 days; range, 4 to 10 days).

The 2 patients whose neurological deficits had improved the least (patients 5 and 8) at the time of discharge were those whose pretreatment clinical deficits were the most severe. Even in these cases, however, symptomatic improvement had occurred at the time of discharge, and long-term outcomes were excellent. It is certainly conceivable that the rapid restoration of flow enhanced the likelihood of favorable outcomes.

Kim and Suh30 published data on similar treatment of 9 patients. Average duration of symptoms before treatment was 29 days (range, 7 to 112 days). Symptoms and signs were headache, seizure, lethargy/somnolence, hemiparesis, and papilledema. Pretreatment MR and CT brain scans were normal in 3 and showed minimal brain swelling and sulcal effacement in 5. Intracerebral hemorrhage (ICH) with venous infarct in the right parietal lobe was present in 1. Mean total dose of rtPA was 135 mg delivered over 20 hours (range, 8 to 43 hours), with concomitant intravenous heparin. Flow was reestablished in all patients, including 1 who had involvement of both convexity and deep systems. No posttreatment brain hemorrhages occurred. According to the authors, “clinical signs and symptoms, including neurologic deficits, seizures, and headaches, were treated successfully in all patients during the 3-month follow-up period.” The duration of hospitalization from the beginning of treatment was not disclosed. There were 2 hemorrhagic complications: (1) groin bleeding requiring no treatment in 1 patient and (2) intraoperative hemorrhage caused by hypofibrinogenemia requiring infusion of fresh-frozen plasma in another patient.

Figure 2. A, From patient 5, CT immediately before treatment revealed a sizable defined area of ischemic/congestive change with subtle hemorrhagic component and mass effect. B, From patient 5, CT 36 hours after treatment revealed no evidence of hemorrhagic transformation.
The results of Kim and Suh\textsuperscript{30} are compatible with ours, although we used much lower doses of rtPA. Both studies document that flow restoration associated with clinical improvement is obtainable in patients whose pretreatment deficits and brain scan changes are minor. The safety and efficacy of this treatment in patients with more severe symptoms and larger ischemic/congestive pretreatment scan changes remain to be determined. The favorable outcome in the 1 patient with hemorrhage treated by Kim and Suh\textsuperscript{30} does not alter our concern about the potential risk of this treatment in patients with more obvious hemorrhage on pretreatment CT scan.

Renowden et al\textsuperscript{31} reported a single patient with SSS and right TS/SS thrombosis who deteriorated while on intravenous heparin. Eight days after symptom onset, a total of 65 mg of rtPA was injected “slowly” into the thrombus. The patient “improved within hours following thrombolysis and 24 hours later the only neurological deficits were bilateral papilledema and bilateral sixth nerve palsies.” Follow-up at 3 months with MRI/MR angiography showed near normal flow of the SSS and almost complete recanalization of the right TS. No complications were reported.

An important consideration in the outcome analysis of our patients and those of Kim and Suh\textsuperscript{30} and Renowden et al\textsuperscript{31} is that only 2 patients had involvement of both convexity and deep venous systems. The prognosis in cases with combined convexity and deep venous system thrombosis is generally poorer.\textsuperscript{3,4,14,25,26,32,33} Treatment of such cases will be technically more problematic than treatment of convexity sinus thrombosis alone.

The use of direct intrathrombus urokinase has been reported in at least 36 patients with CVT. Treatment time was documented in 29 cases, in which results were characterized as technically favorable.\textsuperscript{14,16,17,19,20,22–27} Flow was restored in 26 patients. The average dose of urokinase was 6.14 million units (range, 470k to 13.79 million units). The time required for treatment was 71 hours (range, 1 to 244 hours). Neurological deficits were various, and outcomes were categorized as generally improved/favorable. Hemorrhagic worsening occurred in 2 patients. The hospital cost of urokinase is higher than that of rtPA ($9185 for the average urokinase dose of 6.14 million units versus $1099 for our average of 43 mg rtPA).

A variety of reports imply a benefit of intravenous heparin in patients with CVT.\textsuperscript{5,6,7,34,35} However, the literature contains only 1 randomized controlled study.\textsuperscript{7} In this study, Einhäupl et al treated 10 patients for 21 days with dose-adjusted intravenous heparin and 10 patients with intravenous saline. Pretreatment Glasgow Coma Scale scores were similar for the 2 groups. Neurological outcomes were significantly better in the heparin group at 8 and 21 days, as well as at 3 months. Pretreatment ICH was present in 3 of the heparin-treated patients and in 2 of the control patients. Two ICH patients in the heparin group had no hemorrhagic worsening and recovered completely. The other 1 improved and retained mild neurological deficits. The 2 ICH control patients died.

This study also included a retrospective review of 40 patients who had CVT with ICH. Twenty-seven of these had been treated with dose-adjusted intravenous heparin, and 13 had received no heparin. Of the 27 heparin-treated patients, 4 died, 2 had severe neurological deficits, 7 had mild neurological deficits, and 14 recovered completely. Of the 13 patients who received no heparin, 9 died, 1 had mild neurological deficits, and 3 had complete recoveries. Three additional patients had been treated with “low-dose heparin” with outcomes characterized as “recovered completely” in 2 and “mild neurological deficit” in 1. Unfortunately, definitive conclusions about safety and efficacy of intravenous heparin in patients with CVT and ICH cannot be drawn from these data because assignment to treatment was not randomized, and selection criteria for treatment were not specified.

Although the data for heparin therapy in CVT are generally favorable, the duration of hospitalization is probably longer than that for rtPA plus heparin. In the series by Einhäupl et al,\textsuperscript{7} the time required for treatment was 21 days. Although these data were gathered over 13 years prior to our study and in another country, it has been our own experience that heparin for CVT can rarely be discontinued in less than 1 week. By comparison, treatment time for patients treated with heparin and direct intrathrombus rtPA in our series was 9 days; for patients in whom flow was restored, it was 6.3 days. The case report by Renowden et al\textsuperscript{31} mentioned “improvement in her condition within hours following thrombolysis,” with “repeat [magnetic resonance angiography] MRA 3 days later,” and “discharged a few days later.” Kim and Suh\textsuperscript{30} did not describe hospitalization times after treatment, but the combination of flow restoration and favorable clinical outcomes suggests that they were relatively short. It is certainly conceivable that the combination of heparin and direct intrathrombus rtPA may prove to be cost-effective by virtue of reduced hospitalization times.

The possibility of catheter-mediated thrombectomy in patients with CVT is currently under investigation. Higashida and Furlan\textsuperscript{16} have reported successful technical and clinical results in 1 patient with bilateral transverse sinus thrombosis treated with the “Angiojet” catheter. The utility and cost-effectiveness of this saline jet/vacuum device remain to be studied.

A paramount consideration in any form of anticlotting therapy for CVT is the risk of hemorrhagic worsening. We do not yet have guidelines for the safety of either heparin or rtPA in patients with more obvious hemorrhagic change on brain scan. Although the 3 patients with ICH who received heparin in the series reported by Einhäupl et al\textsuperscript{7} did well, heparin must still be considered a risk for hemorrhagic worsening. Similarly, although the patient with pretreatment hemorrhage in the series by Kim and Suh\textsuperscript{30} did not worsen, the 2 patients with pretreatment hemorrhage in our study did. This must serve as a caution for future testing.

It may be feasible to treat patients who have hemorrhagic lesions with rtPA by placing the catheter tip at a location caudal to the presumed junction of the parenchymal draining vein and the occluded sinus. Conceivably, this strategy would reduce the likelihood of flow or retrograde diffusion of rtPA into the region of hemorrhage, allowing treatment of a more proximal thrombus with lower risk of hemorrhagic worsening.
Conclusions
Our results and those of Kim and Sub\textsuperscript{30} and Renowden et al\textsuperscript{31} with combined intrathrombus rtPA and intravenous heparin in CVT are encouraging. This treatment appears to be safe in patients without obvious pretreatment hemorrhage and has been associated with rapid flow restoration and improved clinical outcomes in 19 of the 22 patients who had no evidence of significant pretreatment hemorrhage on brain scan, and in 1 who did.\textsuperscript{30} The currently available data on rtPA and heparin in CVT suggest a need for further evaluation of this treatment in the form of a comparative trial versus heparin therapy alone. Important issues to be addressed will include patient selection, with special attention to the presence of hemorrhage; treatment strategy, particularly in patients with thrombosis of both convexity and deep venous systems; dosing of rtPA; and assessment of cost-effectiveness. Most important, of course, will be clinical outcomes in CVT are encouraging. This treatment appears to be safe in cerebral venous sinus thrombosis.

References
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